CHAPTER 14.

BASIC RADIOBIOLOGY

NAGALINGAM SUNTHARALINGAM
Department of Radiation Oncology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania, U.S.A.

ERVIN B. PODGORSAK
Department of Medical Physics
McGill University Health Centre
Montréal, Québec, Canada

JOLYON H. HENDRY
Applied Radiation Biology and Radiotherapy Section
Department of Nuclear Sciences and Applications
International Atomic Energy Agency
Vienna, Austria

14.1. INTRODUCTION

Radiobiology, a branch of science that deals with the action of ionizing radiation on biological tissues and living organisms, is a combination of two disciplines: *radiation physics* and *biology*. All living things are made up of protoplasm that consists of inorganic and organic compounds dissolved or suspended in water. The smallest unit of protoplasm capable of independent existence is the *cell*.

- Cells contain inorganic compounds (water and minerals) as well as organic compounds (proteins, carbohydrates, nucleic acids, lipids).
- The two main constituents of a cell are the cytoplasm, which supports all metabolic functions within the cell, and the nucleus, which contains the genetic information (DNA).
- Human cells are either somatic cells or germ cells.
- Cells propagate through division; division of somatic cells is called *mitosis*, division of germ cells *meiosis*.
- When a somatic cell divides, two cells are produced, each carrying a chromosome complement identical to that of the original cell. The new cells themselves may undergo further division and the process continues.

- Somatic cells are classified as:

  - *Stem cells*: exist to self-perpetuate and produce cells for a differentiated cell population (*e.g.*, stem cells of the hematopoietic system, epidermis, mucosal lining of the intestine).
  - *Transit cells*: cells in movement to another population (*e.g.*, a reticulocyte which is differentiating to become an erythrocyte).
  - *Mature cells*: cells that are fully differentiated and do not exhibit mitotic activity (*e.g.*, muscle cells, nervous tissue).

- A group of cells that together perform one or more functions is referred to as *tissue*.

- A group of tissues that together perform one or more functions is called an *organ*.

- A group of organs that perform one or more functions is a *system* of organs or an *organism*.

14.2. CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

For use in radiobiology and radiation protection the physical quantity that is useful for defining the quality of an ionizing radiation beam is the linear energy transfer *(LET)*. In contrast to the stopping power that focuses attention on the energy loss by an energetic charged particle moving through a medium, the *LET* focuses attention on the linear rate of energy absorption by the absorbing medium as the charged particle traverses the medium.

The International Commission on Radiological Units and Measurements (ICRU) defines the *LET* as follows: "*LET of charged particles in a medium is the quotient dE/dl, where dE is the average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of dl*".

In contrast to the stopping power with a typical unit of MeV/cm, the unit usually used for the *LET* is keV / μm. The energy average is obtained by dividing the particle track into equal energy increments and averaging the length of track over which these energy increments are deposited.

- Typical *LET* values for commonly used radiations are:

  - 250 kVp x ray : 2 keV / μm
  - cobalt-60 gamma ray : 0.3 keV/ μm
  - 3 MeV x ray : 0.3 keV/ μm
  - 1 MeV electron : 0.25 keV/ μm

- Values for other less commonly used radiations are:

  - 14 MeV neutrons : 12 keV/ μm
  - heavy charged particles: 100-200 keV/ μm
  - 1 keV electron : 12.3 keV/ μm
  - 10 keV electron : 2.3 keV/ μm

X rays and gamma rays are considered low *LET* (sparsely ionizing) radiations, while energetic neutrons, protons and heavy charged particles are high *LET* (densely ionizing) radiations. The demarcation value between low and high *LET* is at about 10 keV/μm.

14.3. CELL CYCLE AND CELL DEATH

The cell proliferation cycle is defined by two well-defined time periods:

(1) *mitosis M* where division takes place, and
(2) the period of *DNA synthesis S*.

The *S* and *M* portions of the cell cycle are separated by two periods (gaps) G_1 and G_2 when DNA is not yet synthesized but other metabolic processes take place.

- The time between successive divisions (mitoses) is called *cell cycle time*. For mammalian cells growing in culture the *S* phase is usually in the range of 6-8 hours, *M* less than an hour, G_2 in the range of 2-4 hours, and G_1 from 1-8 hours, making the total cell cycle in the order of 10-20 hours. In contrast, the cell cycle for stem cells in certain tissues is up to about 10 days.

- In general, cells are most radiosensitive in the *M* and G_2 phases, and most resistant in the late *S* phase.

- The cell cycle time of malignant cells is shorter than that of some normal tissue cells, but during regeneration after injury normal cells can proliferate faster.

- Cell death for non-proliferating (static) cells is defined as the loss of a specific function, while for stem cells it is defined as the loss of reproductive integrity (reproductive death). A surviving cell that maintains its reproductive integrity and proliferates indefinitely is said to be *clonogenic*.

14.4. IRRADIATION OF CELLS

When cells are exposed to ionizing radiation the standard physical effects between radiation and atoms or molecules of the cells occur first and the possible biological damage to cell functions follows later. The biological effects of radiation result mainly from damage to the DNA which is the most critical target within the cell; however, there are also other sites in the cell which, when damaged, may lead to cell death. When directly ionizing radiation is absorbed in biological material, the damage to the cell may occur in one of two ways: *direct* or *indirect* action.

14.4.1. Direct action in cell damage by radiation

In *direct action* the radiation interacts directly with the critical target in the cell. The atoms of the target itself may be ionized or excited through Coulomb interactions leading to the chain of physical and chemical events that eventually produce the biological damage. Direct action is the dominant process in interaction of high *LET* particles with biological materials.

14.4.2. Indirect action of cell damage by radiation

In *indirect action* the radiation interacts with other molecules and atoms (mainly water, since 80% of a cell is composed of water) within the cell to produce free radicals that can, through diffusion in the cell, damage the critical target within the cell. In interactions of radiation with water short-lived yet extremely reactive free radicals such as H_2O^+ (water ion) and OH• (hydroxyl radical) are produced. The free radicals in turn can cause damage to the target within the cell.

- The free radicals that break the chemical bonds and produce chemical changes that lead to biological damage are highly reactive molecules because they have an unpaired valence electron.

- About two thirds of the biological damage by low *LET* radiations (sparsely ionizing radiations), such as x-rays or electrons, is due to indirect action.

- The indirect action can be modified by chemical sensitisers or radiation protectors.

- For the indirect action of x-rays the steps involved in producing biological damage are as follows:

  Step 1: *Primary photon interaction* (photoelectric effect, Compton effect, pair production) produces a *high energy electron*.

  Step 2: The high-energy electron in moving through tissue produces *free radicals in water.*

  Step 3: The free radicals may produce changes in DNA from *breakage of chemical bonds.*

  Step 4: The changes in chemical bonds result in *biological effects*.

Step (1) is in the realm of physics; step (2) in chemistry; steps (3) and (4) in radiobiology.

14.4.3. Fate of irradiated cells

Irradiation of a cell will result in one of the following four possible outcomes:

(1) No effect

(2) *Division delay*: the cell is delayed from going through division.

(3) *Apoptosis*: the cell dies before it can divide or afterwards by fragmentation into smaller bodies which are taken up by neighbouring cells.

(4) *Reproductive failure*: the cell dies when attempting the first or subsequent mitosis.

14.5. TYPE OF RADIATION DAMAGE

14.5.1. Time scale

The time scale involved between the breakage of chemical bonds and the biological effect may be hours to years, depending on the type of damage.

- If cell kill is the result, it may happen in hours to days when the damaged cell attempts to divide (*early effects* of radiation).
- If the damage is oncogenic (cancer induction), then its expression may be delayed for years (*late effects* of radiation).
- If the damage is a mutation in a germ cell, the effects may not be expressed for generations.
- In addition to carcinogenesis (induction of cancer) the *late effects* of radiation include: (i) life span shortening; (ii) genetic damage, and (iii) potential effects to the fetus. Ionizing radiation has been proven to cause leukemia and has been implicated in development of many other cancers in tissues such as bone, lung, skin, thyroid and breast.

14.5.2. Classification of radiation damage

Radiation damage to mammalian cells is divided into three categories:

(1) *Lethal damage* is irreversible, irreparable, and leads to cell death;

(2) *Sublethal damage* can be repaired in hours unless additional sublethal damage is added and eventually leads to lethal damage; and

(3) *Potentially lethal damage* can be manipulated by repair when cells are allowed to remain in a non-dividing state.

14.5.3. Somatic and genetic effects

The effects of radiation on the human population can be classified as either *somatic* or *genetic.*

- *Somatic effects* are harm that exposed individuals suffer during their lifetime, such as radiation-induced cancers (carcinogenesis), sterility, opacification of the eye lens, and life shortening.
- *Genetic or hereditary effects* are radiation-induced mutations to an individual's genes and DNA that can contribute to the birth of defective descendants.

Carcinogenesis expresses itself as a late somatic effect in the form of acute or chronic myeloid leukemia or some solid tumours, for example, in skin, bone, lung, thyroid or breast. Human data on carcinogenesis have been collected from the following sources:

(1) Low level occupational exposure.
(2) Atomic bomb survivors in Hiroshima and Nagasaki.
(3) Medical radiation exposure to patients (for example, treatment of ankylosing spondylitis, treatment of thyroid abnormalities, radiotherapy of cancer) and staff (for example, radiologists in the early part of last century).

14.5.4. Stochastic and deterministic (non-stochastic) effects

The harmful effects of radiation may be classified into two general categories: *stochastic* and *deterministic* (*non-stochastic*). The NCRP defines these effects as follows:

- A *stochastic effect* is one in which the probability of occurrence increases with increasing dose but the severity in affected individuals does not depend on the dose (induction of cancer, *i.e*., radiation carcinogenesis, genetic effects). There is no threshold dose for effects that are truly stochastic.

- A *deterministic* (*non-stochastic*) *effect* is one which increases in severity with increasing dose, usually above a threshold dose, in affected individuals (organ atrophy, fibrosis, lens opacification, blood changes, decrease in sperm count).

14.5.5. Acute vs. chronic effects

An organ or tissue expresses response to radiation damage either as an *acute effect* or as *late (chronic) effect.*

- Acute effects manifest themselves soon after exposure to radiation and are characterized by inflammation, edema, denudation of epithelia and hemorrhage.

- Chronic effects are delayed and are characterized by fibrosis, atrophy, ulceration, stenosis or obstruction of the intestine.

14.5.6. Total body radiation response

The response of an organism to acute total body radiation exposure is influenced by the combined response to radiation of all organs constituting the organism. Depending on the actual total body dose above 1 Gy, the response is described as a specific radiation syndrome:

- 1 Gy < Dose < 10 Gy: *bone marrow syndrome*
- 10 Gy < Dose < 100 Gy: *gastrointestinal (GI) syndrome*
- Dose > 100 Gy: *central nervous system (CNS) syndrome*

Human data on specific radiation syndromes have been collected from the following sources:

- Accidents in industry and research laboratories
- Accidents involving exposure from radioactive fallout from nuclear testing of weapons or the Chernobyl nuclear power plant accident
- Exposure of humans to high levels of radiation in Hiroshima and Nagasaki
- Medical exposure of humans to total body irradiations

14.5.7. Fetal irradiation

Between conception and birth the fetus passes through three basic stages of development:

- *pre-implantation* (day: 1 to 10);
- *organogenesis* (day: 11 to 42); and
- *growth stage* (day: 43 to birth).

Radiation is a known teratogen (*i.e.*, it causes birth defects).

- The effects of radiation on the fetus depend on two factors: dose and stage of development at the time of exposure.

- The principal effects of radiation on a fetus are: fetal or neonatal death, malformations, growth retardation, congenital defects, and cancer induction.

- An abortion to avoid a possibility of radiation-induced congenital abnormalities should be considered only when the fetal dose has exceeded 10 cGy. For doses exceeding 25 cGy an abortion is recommended.

14.6. CELL SURVIVAL CURVES

A *cell survival curve* describes the relationship between the surviving fraction of cells, *i.e.*, the fraction of irradiated cells that maintain their reproductive integrity (clonogenic cells), and the absorbed dose.

- Cell survival as a function of radiation dose is graphically represented by plotting the surviving fraction on a logarithmic scale on the ordinate against dose on a linear scale on the abscissa.

- Cell surviving fractions are determined with *in-vitro* or *in-vivo techniques*. Examples of survival curves for irradiation of cells by densely (A) and sparsely (B) ionizing radiation beams are sketched in Fig. 14.1.

The type of radiation influences the shape of the cell survival curves. Densely ionizing radiations exhibit a cell survival curve that is almost an exponential function of dose, shown by almost a straight line on the log-linear plot. For sparsely ionizing radiation, on the other hand, the curves show an initial slope followed by a shoulder region and then become nearly straight at higher doses. Factors that make cells less radiosensitive are: removal of oxygen to hypoxic state, the addition of chemical radical-scavengers, the use of low dose-rates or multifractionated irradiation, and cells synchronized in the late-S phase of the cell cycle.

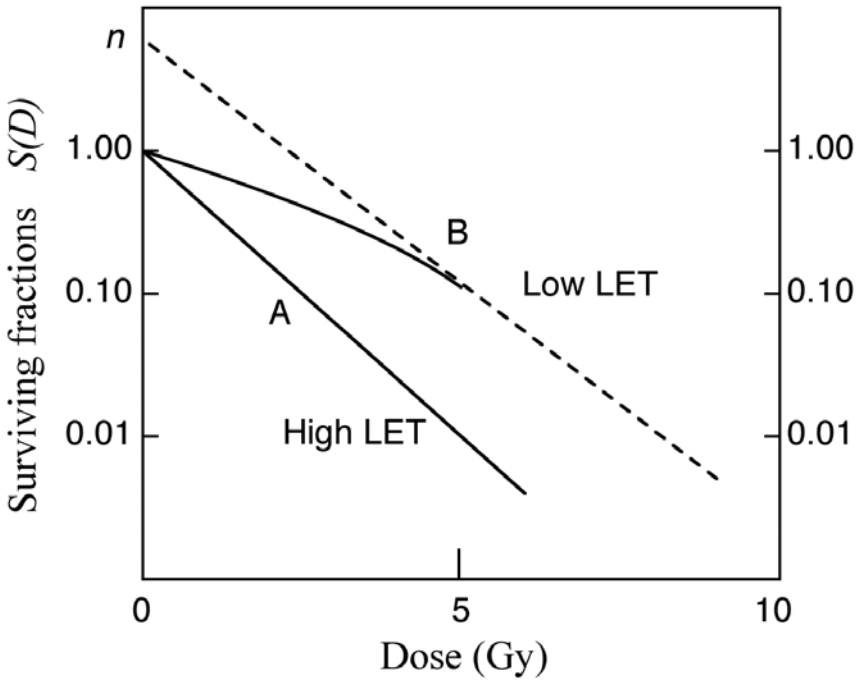

FIG. 14.1. Sketch of typical cell survival curves for (A) high LET (densely ionizing) radiation and (B) low LET (sparsely ionizing) radiation.

Several mathematical methods of varying degrees of complexity have been developed to define the shape of cell survival curves, all based on the concept of random nature of energy deposition by radiation.

- The ***linear-quadratic model*** is now most often used to describe the cell survival curve assuming that there are two components to cell kill by radiation:

$$S(D) = e^{-\alpha D - \beta D^2} \quad , \tag{14.1}$$

where

$S(D)$ is the fraction of cells surviving a dose D,
α is a constant describing the initial slope of the cell survival curve, and
β is a smaller constant describing the quadratic component of cell killing.

- The ratio α / β gives the dose at which the linear and quadratic components of cell killing are equal.

- For completeness, the earlier multi-target single-hit model described the slope of the survival curve by Do (the dose to reduce survival to 37% of its value at any point on the final near-exponential portion of the curve) and the extrapolation number (the point of intersection of the slope on the log-survival axis). However, this model does not have any current biological basis.

14.7. DOSE-RESPONSE CURVES

A plot of a biological effect observed (*e.g.*, tumour induction, tissue response) against the dose given is called a dose-response curve. Generally, as dose increases so does the effect.

- Three types of dose-response relationships are known:

  - *Linear*;
  - *Linear-quadratic*;
  - *Sigmoid*.

- The dose-response curves may or may not have a threshold. A threshold dose is the largest dose for a particular effect studied, below which no effect will be observed.

Various dose response curves are sketched in Fig.14.2 with:

(A) linear relationship-no threshold;
(B) linear relationship with threshold;
(C) linear-quadratic relationship-no threshold;
(D) linear relationship (area below the dashed line indicates natural incidence of the effect);
(E) sigmoid relationship with threshold.

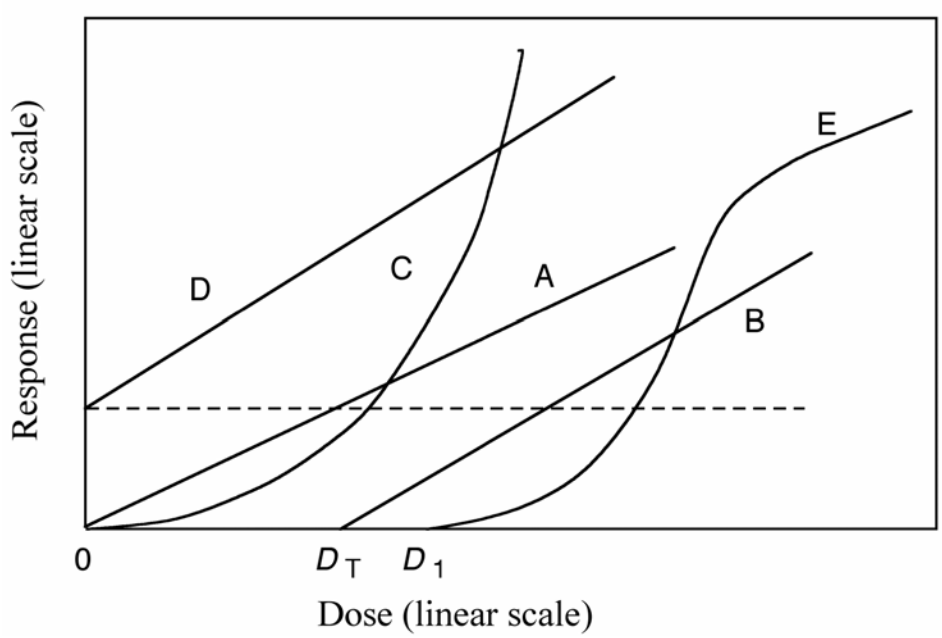

FIG. 14.2. Sketch of typical dose response curves for cancer induction (curves A, B, C, D) and for tissue response (curve E). Curve (A) represents linear relationship - no threshold; curve (B) linear relationship with threshold D_T; curve (C) linear-quadratic relationship - no threshold (assumed for stochastic effects, e.g., carcinogenesis); curve (D) linear relationship-no threshold (area below dashed line represents the natural incidence of the effect, e.g., carcinogenesis); and curve (E) sigmoid relationship with threshold D_1, as is common for deterministic effects in tissues, e.g., tumour control, treatment morbidity.

The response of different tissues or organs to radiation varies markedly, depending primarily on two factors:

(1) Inherent sensitivity of the individual cells
(2) Kinetics of the population.

There is a clear distinction in radiation response between tissues that are *early responding* (skin, mucosa, intestinal epithelium) and those that are *late responding* (spinal cord), as shown schematically in Fig. 14.3 for the surviving fraction against the dose.

- The cell survival curves for the late responding tissues are more curved than those for the early responding tissues.
- For early effects the ratio α/β is large and α dominates at low doses.
- For late effects α/β is small and β has an influence even at low doses.
- The two components for mammalian cell killing are equal at approximately 10 Gy and 2 Gy for early and late effects, respectively.

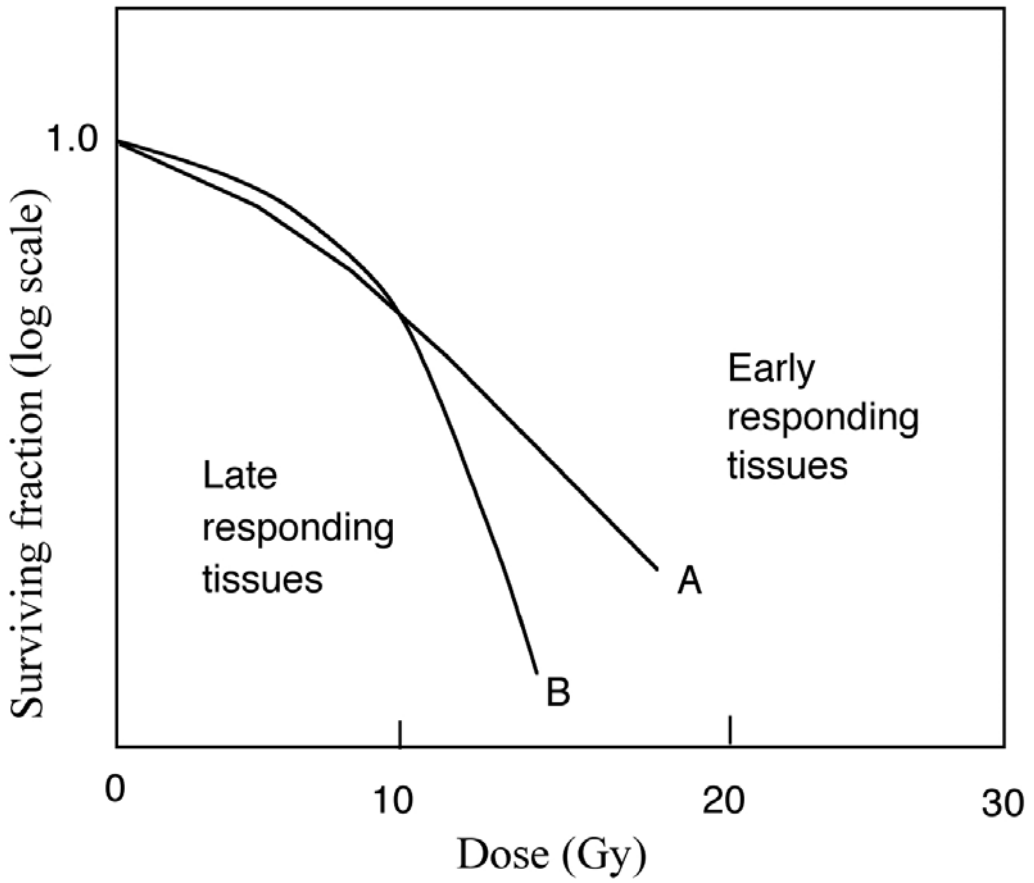

FIG. 14.3. Sketch of typical cell survival curves for (A) early responding tissues and (B) for late responding tissues.

14.8. MEASUREMENT OF RADIATION DAMAGE IN TISSUE

The effects of radiation on tissue as a function of dose is measured with assays and the measurement results are given in the form of cell survival curves or dose response curves. Three categories of tissue assays are in use:

(1) *Clonogenic assays* measure the reproductive integrity of the clonogenic stem cells in tissue and the measurements result in cell survival curves.

(2) *Functional assays* measure functional end-points for various tissues and produce dose response curves, where the response is measured on a graded reaction scale or expressed as a proportion of cases where reactions are greater than a specified level.

(3) *Lethality assays* quantify the number of animal deaths after irradiation of a specific organ with a given dose. The experiments usually result in deduced values of the parameter LD_{50} defined as the (lethal) dose to a specific organ that kills 50% of the animals.

14.9. NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

The aim of radiotherapy is to deliver enough radiation to the tumour to destroy it without irradiating normal tissue to a dose that will lead to serious complications (morbidity). As shown in Fig. 14.4, the principle is usually illustrated by plotting two sigmoid curves, one for the *tumour control probability* (*TCP*, curve A) and the other for *normal tissue complication probability* (*NTCP*, curve B).

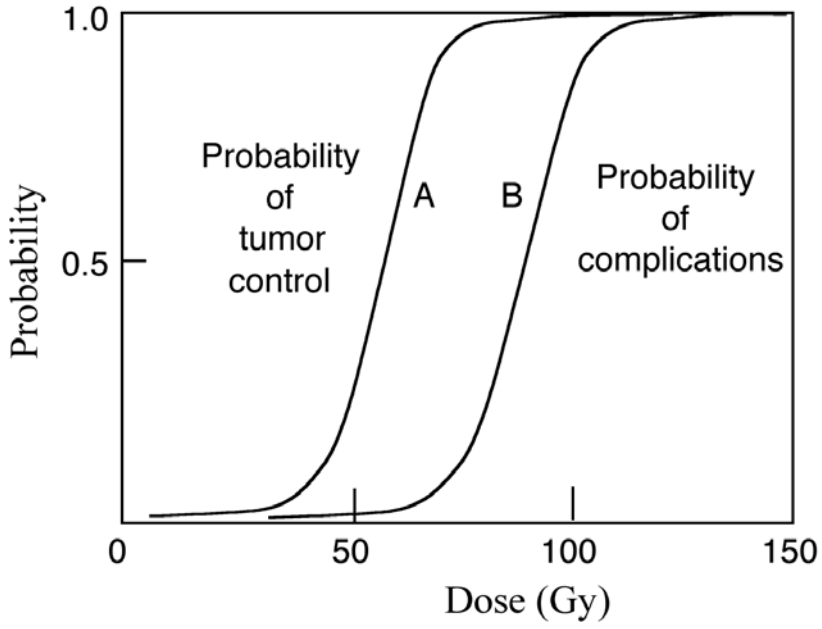

FIG. 14.4. The principle of therapeutic ratio. Curve (A) represents the tumour control probability, curve (B) the probability of complications. The total dose is delivered in 2 Gy fractions.

- The optimum choice of radiation dose delivery technique in treatment of a given tumour is such that it maximizes the *TCP* and simultaneously minimizes the *NTCP*. For a typical radiotherapy treatment, $TCP \geq 0.5$ and $NTCP \leq 0.05$.

- The farther is curve B (*NTCP*) to the right of curve A (*TCP*) in Fig. 15.4, the easier it is to achieve the radiotherapeutic goal, the larger is the so-called *therapeutic ratio*, and the less likely will be that the treatment causes complications.

- The therapeutic ratio generally refers to the ratio of *TCP* and *NTCP* at a specified dose level; however, it is also often defined as the ratio of doses at a specified level of response (usually 0.05) for normal tissue.

- Figure 14.4 shows an ideal situation; in reality, the *NTCP* curve is often shallower than the *NTCP* curve. Moreover, the *TCP* curve in certain tumours never reaches a value of 1.0 as a result of microscopic or metastatic spread of the disease beyond the primary tumour site. It is thus imperative that the average doses to normal tissues be kept lower than the doses to tumours in order to minimize treatment complications and optimize treatment outcomes. In modern radiotherapy this is achieved through sophisticated 3-dimensional treatment planning (forward or inverse) and dose delivery (conformal or intensity-modulated).

- In the early days of radiotherapy it was usually assumed that normal cells were less sensitive to radiation than tumour cells; however, currently it is accepted that both malignant and normal mammalian cells responsible for early reactions exhibit similar values for D_o around 1.3 Gy.

- It is for late reactions that the shoulder on the cell survival curve is effectively greater than it is for tumours or early-reacting tissues, so providing a differential that is exploited in hyperfractionation protocols.

- The therapeutic ratio varies with many factors, such as the dose-rate and LET of the irradiation, the presence of radiosensitizers or radioprotectors, the design of treatment plan, and the precision of implementation of the treatment plan.

14.10. OXYGEN EFFECT

The presence or absence of molecular oxygen within a cell influences the biological effect of ionizing radiation: the larger the cell oxygenation above anoxia, the larger is the biological effect until saturation of the effect of oxygen occurs, especially for low *LET* radiations. As shown in Fig. 14.5, the effect is quite dramatic for low *LET* (sparsely ionizing) radiations, while for high *LET* (densely ionizing) radiations it is much less pronounced. The ratio of doses without and with oxygen (hypoxic vs. well-oxygenated cells) to produce the same biological effect is called the oxygen enhancement ratio *(OER).*

$$OER = \frac{Dose\ to\ produce\ a\ given\ effect\ without\ oxygen}{Dose\ to\ produce\ the\ same\ effect\ with\ oxygen} \tag{14.2}$$

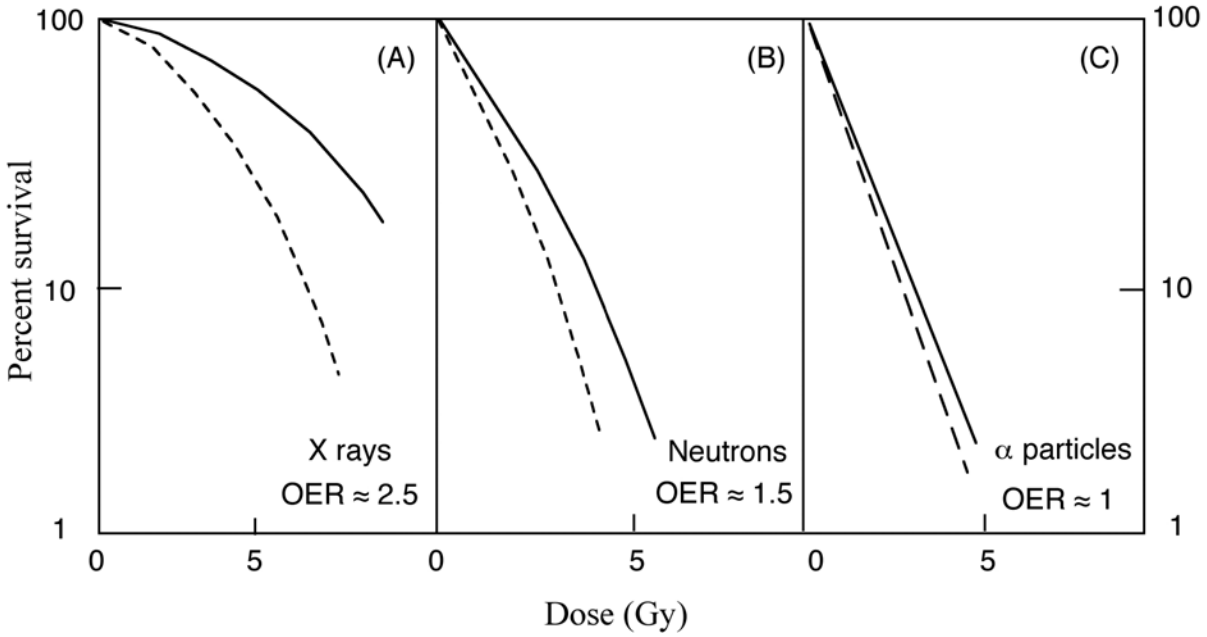

FIG. 14.5. Typical cell surviving fractions for x rays, neutrons and α particles: dashed curves are for well oxygenated cells, solid curves for hypoxic cells.

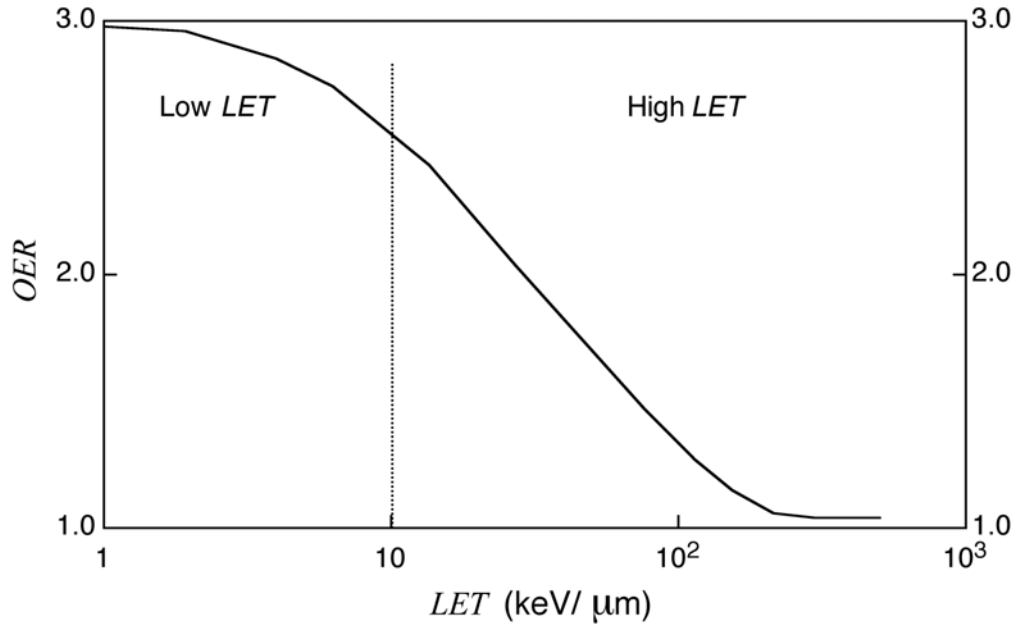

FIG. 14.6. Oxygen enhancement ratio (OER) against LET. The vertical dashed line separates the low LET region where LET <10 μm from the high LET region where LET > 10 μm.

- The *OER* for x-rays and electrons is about 3 at high doses and falls to about 2 for doses of 1 to 2 Gy.
- The *OER* decreases as the *LET* increases and approaches *OER* = 1 at about *LET* = 150 keV/μm , as sketched in Fig. 14.6.
- Reoxygenation is the process by which cells that are hypoxic during irradiation become oxygenated afterwards.

14.11. RELATIVE BIOLOGICAL EFFECTIVENESS

As the LET of radiation increases, the ability of the radiation to produce biological damage also increases. Relative biological effectiveness *(RBE)* compares the dose of test radiation to the dose of standard radiation to produce the same biological effect. The standard radiation is usually taken as 250 kVp x rays for historical reasons. *RBE* is defined by the following ratio:

$$RBE = \frac{Dose\ from\ standard\ radiation\ to\ produce\ a\ given\ biological\ effect}{Dose\ from\ test\ radiation\ to\ produce\ the\ same\ biological\ effect}. \qquad (14.3)$$

- *RBE* varies not only with type of radiation but also with type of cell or tissue, biologic effect under investigation, dose rate and fractionation.
- In general, *RBE* increases with *LET* to reach a maximum *RBE* of 3 to 8 (depending on the level of cell kill) at $LET \approx 200$ keV/μm and then decreases, as sketched in Fig. 14.7.
- An increase in the RBE in itself offers no therapeutic advantage, unless there is a differential effect making the RBE for normal tissue smaller than that for the tumour, increasing the relative level of tumour cell killing and the therapeutic ratio.

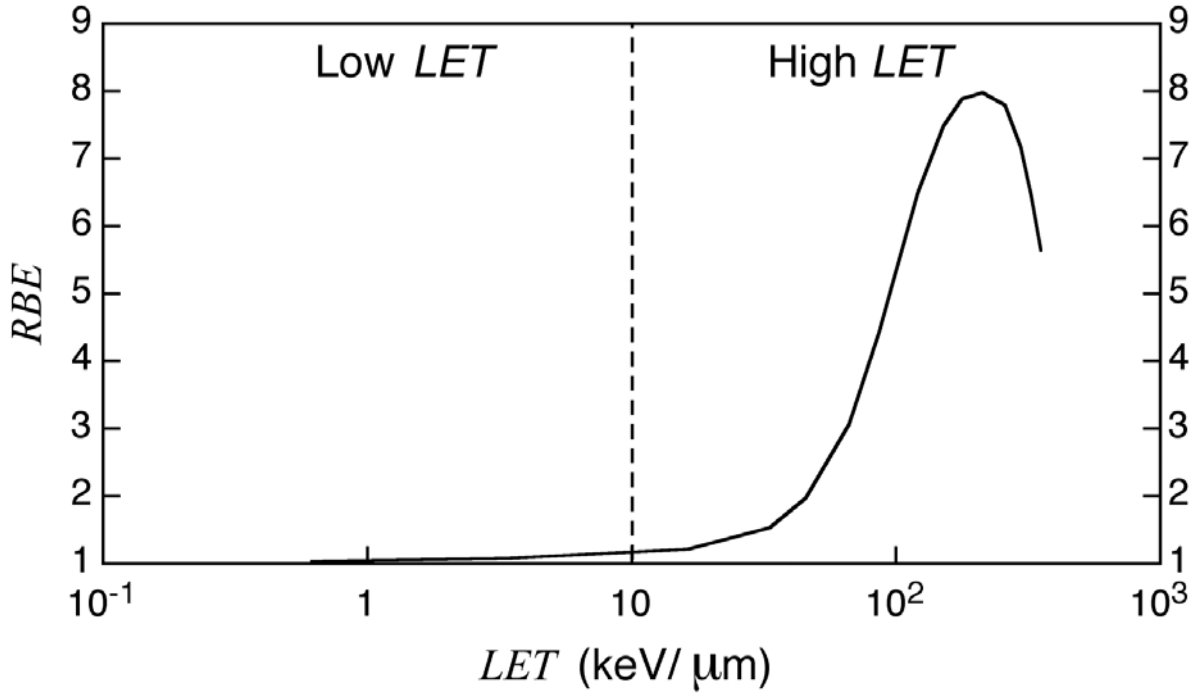

FIG. 14.7. Relative biological effectiveness (RBE) against LET. The vertical dashed line separates the low LET region where $RBE \approx 1$ *from the high LET region where RBE first rises with LET, reaches a peak of about 8 for* $LET \approx 200$ keV/μm *and then drops with a further increase in LET.*

14.12. DOSE RATE AND FRACTIONATION

For the same radiation dose, radiation delivered at a lower dose rate may produce less cell killing than radiation delivered at a higher dose rate because sublethal damage repair occurs during the protracted exposure. As the dose rate is reduced, the slope of the survival curve becomes shallower and the shoulder tends to disappear, since in the linear-quadratic model α does not change significantly; however, $\beta \to 0$.

The typical *dose rates* used in radiotherapy are of the order of:

- 1 Gy/min in standard radiotherapy and high dose rate (HDR) brachytherapy
- 0.1 Gy/min in total body irradiation
- 0.01 Gy/min in low dose rate (LDR) brachytherapy

Fractionation of radiation treatment so that it is given over a period of weeks rather than in a single session results in a better therapeutic ratio. However, to achieve a desired level of biological damage the total dose in a fractionated treatment must be much larger than that in a single treatment.

The basis of fractionation is rooted in five primary biologic factors called the five Rs of radiotherapy:

(1) *Radiosensitivity*. Mammalian cells have different radiosensitivities.

(2) *Repair*. Mammalian cells can repair radiation damage. This is a complex process that involves repair of sublethal damage by a variety of repair enzymes and pathways.

(2) *Repopulation***.** Cells repopulate while receiving fractionated doses of radiation.

(3) *Redistribution* in proliferating cell population throughout the cell cycle increases the cell kill from fractionated treatment relative to single session treatment.

(4) *Reoxygenation* of hypoxic cells during a fractionated course of treatment, making them more radiosensitive to subsequent doses of radiation.

Conventional fractionation is explained as follows: dividing of dose into multiple fractions spares normal tissues through a *repair* of sub-lethal damage between dose fractions and *repopulation* of cells. The former is greater for late-reacting tissues, and the latter for early-reacting tisues. Concurrently, fractionation increases tumour damage through *reoxygenation* and *redistribution* of tumour cells. A balance is achieved between the response of tumour and early- and late-reacting normal tissues, so that small doses per fraction spare late reactions preferentially, and a reasonable schedule-duration allows regeneration of early-reacting tissues and tumour reoxygenation to likely occur.

The current standard fractionation is based on 5 daily treatments per week and the total treatment time of several weeks. This regimen reflects practical aspects of dose delivery to a patient, successful outcome to patient treatments, and convenience to staff delivering the treatment.

Other fractionation schemes are studied with the aim of improving the therapeutic ratio. Some of these are: *hyperfractionation*, *accelerated fractionation*, and *CHART*.

- *Hyper-fractionation* uses more than one fraction per day with a smaller dose per fraction (<1.8 Gy) to reduce long-term complications and to allow delivery of higher total tumour dose.

- *Accelerated fractionation* reduces the overall treatment time minimizing tumour cell proliferation during the course of treatment.

- *CHART* (continuous hyper-fractionated accelerated radiotherapy) is an experimental program used with 3 fractions per day, for 12 continuous days.

14.13. RADIOPROTECTORS AND RADIOSENSITIZERS

Various chemical agents may alter the cell response to ionizing radiation, either reducing or enhancing the cell response.

- Chemical agents that reduce cell response to radiation are called *radioprotectors.* They generally influence the indirect effects of radiation by scavenging the production of free radicals. The dose modifying factor *(DMF)* is defined as follows:

$$DMF = \frac{Dose\ to\ produce\ an\ effect\ with\ radioprotector}{Dose\ to\ produce\ same\ effect\ without\ radioprotector}. \qquad (14.4)$$

- Chemical agents that enhance the cell response to radiation are called *radiosensitizers* generally promoting both the direct and indirect effects of radiation. Examples are halogenated pyrimidines that intercalate between the DNA strands and inhibit repair, and hypoxic cell radiosensitisers which act like oxygen.

- Another type of radiosensitizer are compounds containing boron that enhances the effects of thermal neutron radiation therapy. Boron-10 has a high cross-section for reaction with thermal neutrons (kinetic energy of the order of 0.025 eV). When a thermal neutron interacts with boron-10, an unstable nuclide boron-11 is formed that undergoes fission and produces α particles delivering a high dose in the immediate vicinity of the compound that contains boron. The boron neutron capture therapy (BNCT) has been investigated since the 1950s; however, successful clinical applications have so far been elusive.

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